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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re patent application of
A.V. Schally, et al.

Serial No.: 09/547,215
Confirmation No.: 4694

Filed: April 11, 2000

For: ANTAGONISTIC ANALOGS OF GH-RH INHIBITING IGF-I and -II

Group art: 1642

Examiner: Yu, Misook

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BRIEF ON APPEAL

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Table of Contents

Table of Cases Cited

Real Party in Interest

The title to this application is heald by the Trustees of the Tulane Educational Fund (Tulane University). The Veterans Administration of the United States Government has certain rights to the invention claimed therein as does Zantaris AG, a Corporation of Germany, having a place of business at Weissmueller Strasse, Frankfurt, Germany.

Related Appeals and Interferences

None

Status of Claims

Claims 9-17 are in the application. Claims 9-13, 16 and 17 have been rejected. Claim 11 is beleived to be allowable under 35 U.S.C 112 if amended as per attached amendment. Claims 14 and 15 are objected to but would be allowable if written in independent form including all limitations of rejected claim 10 on which they depend. All claims (9-17) are on appeal.

Status of Amendments

An amendment to reduce the issues on appeal with respect to claim 11 only, is filed contemporaneously herewith. Appellants request correction of the lack of antecedent basis in said claim.

Summary of the invention

The claims of the present invention are directed to three modes of therapeutic use of a group of novel peptides. The peptides themselves were previously claimed in the parent application hereof and the claims thereto issued in US Patent 6 057 422.

Thirty preferred novel peptides included within the scope of the three generic claims are listed at page 10 line 25 through page 12 line 22, with the 6 particularly preferred peptides listed at page12 line 25 through page 13 line 11. The syntheses of the 30 Compounds is set forth in Examples i and II, however since the patentability of the compounds themselves in not believed to be in issue here further discussion thereof is not being set forth

The invention is summarized from page 4 line 20 through page 7 line 20. In view of the arguments to be set forth below, the attention of this Honorable Board is particularly drawn to the section entitled *D. Pharmaceutical compositions* (page 18 line 18 through page 19 line18) taken both *per se* and in conjunction with the following section *E Therapeutic Uses etc* (page 19 line 20 through page 22 line 9).

Attention is also directed to test results carried out on a substantial number of peptides within the scope of generic claims 9-11 set forth as to biological activity in Example III (page 24 line 6 through page 31 line 19) and the accompanying Tables II through IV (page 19 line 21 through page 34 line 20). The significance of somewhat less broad testing of oncological activity at Example IV and the accompanying Tables V through IX (Page 34 line 22 through page 38 line 27) should also be noted.

The relationship of the figures to the tables set forth above is as follows

Figure	Table
I	V
II	VI
III	VII
IV	VIII
V	IX

Issues

1. Whether claims 9, 12 and 13 are unpatentable under 35 U.S.C. 112 first paragraph for insufficient enablement.

2. Whether Claim 10 is unpatentable under 35 U.S.C. 112 first paragraph for insufficient enablement with respect to all peptides set forth therein except for peptide 1 and 3.

3. Whether Claims 11, 16 and 17 are unpatentable under 35 U.S.C. 112 first paragraph for insufficient enablement.

4. Whether Claims 11, 16 and 17 are unpatentable under 35 U.S.C. 112 first paragraph on the ground that that the specification does not convey to one skilled in the art that applicants were in possession of the invention at the time the application was filed.

5. Whether claims 9-11 are unpatentable under 35 U.S.C. 103 (a) over WO 95/16707 (1922June 1995) and Sato et al (1990, Biochem.Biophys. Res Commun. 167, 360-336).

Grouping of Claims

No change requested.

Argument

1. Whether claims 9, 12 and 13 are unpatentable under 35 U.S.C. 112 first paragraph for insufficient enablement

It is not clear from the outstanding Official Action whether the rejection is based on the language of "effective amount" or "patient in need of same" of the rejection is based on lack of support for this language in the specification. For the sake of completeness however both question will be considered herein. This issue was considered in *In re Gardner* 57 CCPA 1207, 1427 F.2d 786; 166 USPQ 138 (1970). The Court (at 1211) reversed the decision of this Honorable Board holding that the use of the former term was indefinite. It would appear that the Examiner, while not using that term *ipsis verbis*, is in fact basing her rejection on the same ground. The Court held that the term, although broad was not indefinite, citing, with approval *In re Caldwell* 50 CCPA 1464, 319 F.2d 254; 138 USPQ 243 (1963) and *In re Halleck* 57 CCPA 954, 422 F.2d 911; 164 USPQ 647 (1970). The court further held that the dosage range of 10 mg to 100 or 150 mg totally adequate as to definiteness even though the range was broad. The present case recites ranges of similar breadth in the specification.

The *Gardner* Court then went on to consider whether the claims met the requirements of the first paragraph of 35 USC 112 with respect to adequacy of disclosure, which is the second question to be determined under the present heading. While the Court in *Gardner* found that the requirements of the statute were not met in that case, those circumstances can be readily distinguished in the present case where they meet the Court's criteria.

In *Gardner* , no host is mentioned. In the present application it is explicitly stated (at p.18 line 27) that the host may be human or animal. In *Gardner* there was no animal test data and above all no dosage theory. The Examiner acknowledges the presence of a wealth of test data herein , but argues that this is inadequate under 35USC 112, first paragraph, Appellants respectfully disagree and point out (at p.19 lines 17 & 18) the dosage range is stated in terms of µg/kg of body weight. This indication is as much as can be expected at this point.

Appellants point of view is well supported by the precedent of case law after *Gardner.* An issue similar to that herein was under consideration in *In re Gordon L. Bundy* 642 F2.2d 430; 1981 CCPA 254: 209 U.S.P.Q 48 (1981) in which the Court upheld appellants view of adequacy of enablement. There were several issues in this area in that case Discussing the adequacy of "how to use" (at 434-) the Court noted that the case involved novel analogs of E-type prostaglandins. Not only were there no examples of dosages or even animal tests for the compounds. This is in contract to the present situation where both appear in the specification. The specification disclosed broad ranges of dosages for the E-type prostaglandins. It was only at oral argument that appellants' counsel indicated that at the time of filing, all that had been established was

the basic pharmacology. The court held that this was enough to enable one skilled in the art to determine the specific dosages. While this case deals with compounds not methods of use, the principle applies and the present situation is taken out of the "compounds only" situation by the extensive animal testing and une4xpected showing of superiority of the compounds to be used in the present claims which are discussed in detail with respect to the 35 U.S.C. 103 rejection dealt with hereinbelow.

The Examiner is respectfully reminded that this is not an NDA at the FDA. It takes up to a decade and the expenditure of at least tens of millions of dollars to generate the sort of information she mistakenly considers is required under 35 USC 112 to satisfy patentability. It should be noted that the *Bundy* court (at 434 last paragraph) agrees with this position, clearly ststing that the "early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged".

The attention of this Honorable Board is drawn to a more recent case in this area of law (again a "compound" rather than a "method of use " case) *In re Miguel F. Brana et al.* 51 F.3rd 1560; 1995 U.S. App 6363; 34 U.S.P.Q 2D 1436(1995). The Court deals extensively with the case law of enablement under 35 U.S.C 112, discussing the issue initially at p. 1566.

This court's predecessor has stated in *In re Marzocchi,* 58 C.C.P.A. 1069; 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971) that:

> A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must*** be taken as in compliance with the enabling requirement of the first paragraph of § 112 ***unless*** there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. 439 F.2d at 224, 169 U.S.P.Q.370 only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy* 642 F.2d 430; 209 U.S.P.Q. 48, 51 (CCPA 1981).

See also *In re Novak* 49 C.C.P.A. 1283, 306 F.2d 924, 928, 134 U.S.P.Q. 335, 337(CCPA 1962) (stating that it is proper for the examiner to request evidence to substantiate an asserted utility unless one with ordinary skill in the art would accept the allegations as obviously valid and correct); *In re Chilowsky,* 43 C.C.P.A. 775, 229 F.2d 457, 4~62, 108 U.S.P.Q. (BNA) 321, 325 (CCPA 1956) ("Where the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry . . . no further evidence is required."). But see *In re Marzocchi,*

439 F.2d at 223, 169 U.S.P.Q. at 369-70 ("In the field of chemistry generally there may be times when the well- known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles.").

The question of "undue experimentation has been considered by the Federal Circuit.

Explaining what is meant by "undue experimentation," the Federal Circuit has stated that

> "the test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention." *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed.Cir. 1996) (quotation and citation omitted); *see also In re Wands*, 858 F.2d 731, 736-40 (Fed. Cir. 1988) ("The key word is 'undue,' not 'experimentation'") (quoting *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)).
>
> The factors that may be considered in determining whether a disclosure would require undue experimentation include :
>
> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Wands*, 858 F.2d at 737.
>
> All of the [*Wands*] factors need not be reviewed when determining whether a disclosure is enabling." *Enzo Biochem, Inc. v. Calgene, Inc. ("Calgene")*, 188 F.3d 1362, 1371 (Fed. Cir. 1999); *see Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir.) (noting that these factors "are illustrative, not mandatory. What is relevant depend on the facts"), *cert. denied*, 502 U.S. 856 (1991).
>
> Appellant submits that it is clear that appellant has met all of the foregoing standards while the Examiner has not.

Brana is interesting for the very generous standard the Court set for meeting the enablement requirement, which is more than exceeded by Appellants' specification.

The *Brana* enablement segments merely state that:

"We have found that (listing the compounds), and their salts with physiologically tolerated acids have a better action and a better action spectrum as antitumor substances"

The compounds according to the invention can be administered in a conventional manner, orally or parenterally. They can be used in the conventional solid or liquid pharmaceutical form, for example as tablets, film tablets, capsules, granules, coated tablets or solutions. These are prepared in a conventional manner, and to do so the active compounds are mixed with the conventional pharmaceutical auxiliaries, such as tablet binders, fillers, preservatives, tablet disintegrators, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, retarding agents and/or antioxidants (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978). The administration forms thus obtained normally contain the active compound in an amount of from 10 to 90% by weight"

Claims 9, 12, and 13 clearly meet the standards required by the Court with respect to enablement and the rejection of these claims by the Examiner should be reversed.

The statutory and constitutional basis of the patent system is to encourage the useful arts by making new knowledge available as quickly as possible. Indeed the present policy of the USPTO in requiring publication of applications before grant (unless foreign filing is waived) indicates how seriously this provision of rapid disclosure is being taken. If the criteria of detailed pharmacological data were indeed to be required, an inventor would be faced with either the Scylla of wild guesses, which if incorrect might well invalidate the claims or the Carybidis of not applying for a method of use patent until the detailed data was available. In the latter case the application would probably never be allowed since such claims would be held unpatentable for obviousness under 35 USC 103 over the inventor's own patent for the compositions, which would already have issued years previously. Clearly neither of these alternatives are viable in a practical world and thus the Examner's bases of rejection are untenable.

2. Whether Claim 10 is unpatentable under 35 U.S.C. 112 first paragraph for insufficient enablement with respect to all peptides set forth therein except for peptide 1 and 3.

It is Appellants' position that based on the precedents cited in Section 1 of this argument, as set forth above. The burden of showing enablement has clearly been met. The superiority of a substantial number of the compounds in question has clearly been met by the very extensive testing in vitro as well as in vivo. Appellants are not required to show that each an every compound involved in the method claims is efficacious within the outlines set forth in the specification. On the contrary, the Examiner is required to provide evidence to support her position. No evidence has been produced.

The Examiner has just cited the position of certain scientific publications in related areas which indicate that uncertainty might exist. This is not evidence. As stated above, at the strategy of development of the invention at time of filing Appellants have met their burden under the Statute.

3. Whether Claims 11, 16 and 17 are unpatentable under 35 U.S.C. 112 first paragraph for insufficient enablement.

It is Appellants' position that the discussion bridging pages 21-22 of the specification establish the utility of GHRH antagonists in inhibiting IGF II protein and IGF II mRNA levels in cancer cells. Thus since a substantial number of the compounds named in these claims are shown to have excellent antagonistic activity it is submitted that the standards discussed above in paragraph 1 of this argument have been met and the Examiner's rejection of these claims should be reversed.

4. Whether Claims 11, 16 and 17 are unpatentable under 35 U.S.C. 112 first paragraph on the ground that that the specification does not convey to one skilled in the art that applicants were in possession of the invention at the time the application was filed.

It is appellants position that the disclosure of the specification at page 18 line 18 through page 19 line 18 is entirely adequate under 35 U.S.C 112 as interpreted by the various decisions of the Court set forth in Paragraph 1 of this argument. It has been repeatedly reiterated by the Court as well as by the USPTO Guidelines for Asserted Therapeutic or Pharmacological Utilities (M.P.E.P. 2107.03), that the level of detail of administration alledgedly needed as sted by the examiner, is not required.

The Examiner should be reminded that a scientifically credible invention is patentable without any experimental detail whatsoever. The present application is replete with experimental detail. It is the result of painstaking work by a group of scientists of worldwide repute who are not known to make unfounded statements. The Appellants were clearly in possession of enough of the claimed invention to meet the standards discussed in paragraph 1 of this argument. The Examiner's position should be reversed and all claims rejected by her under 35 U.S.C. 112 should be considered allowable under that section.

5. Whether claims 9-11 are unpatentable under 35 U.S.C. 103 (a) over WO 95/16707 (22June 1995) and Sato et al (1990, Biochem.Biophys. Res Commun. 167, 360-336).

Appellants respectfully traverse the examiners arguments as to unpatentability of these claims as under 35 USC 103 (a). While it is understood that an Examiner is not bound by the decision of an Examiner in ANOTHER application it is respectfully submitted this is not a general situation. The Examiner in the case, of which the present application is a DIVISIONAL, found that the compounds, which form the basis of the presently disputed method of use claims, were indeed patentable. The present examiner has advanced no reasons as to why her predecessor was incorrect in her decision.

While inconsistent pleading is permissible in the Federal Courts, appellants submit that the Examiner cannot have it both ways. She cannot argue that under 35 USC 112 the claims are so broad as to invite undue experimentation (a position which has been argued above as being untenable anyway) and argue in the present matter that the compounds utilized in the claims herein for the uses claimed would be obvious and their utility would be obvious. It is not clear to appellants whether the Examiner is arguing that the compounds are obvious or their uses are obvious. Clearly in order to determine whether the use is obvious, the compounds, which are to be used, must first be available. The compounds do not become available until they are made. Thus inherently the compounds must either be available before the invention claimed herein (which clearly they were not) or it must have been obvious to make them in order to invent their claimed use. Thus before determining if the use was obvious, the provision of the compounds must have been obvious. It is applicants position that neither the first nor the second criteria have been met in the Examiner's argument.

Appellants do not dispute the content of the WO95/16707 and Sato disclosures. However applicants most vigorously dispute that these disclosures either per se or in combination would lead one skilled in the art to make the compounds in question and claim their use as set forth in the present application.

The point at issue here is NOT the use of certain compounds in the GENERAL categories disclosed by WO95/16707 and Sato, but rather which compounds have certain highly desirable and unpredicted properties. The Examiner has not dealt with this issue.

Attention is drawn to Tables II, III, IV, VII and Figure III of the present application, and Tables II, III, IV, and V in the WO 95/16707 disclosure.

The issue in Table II is directed to the relative time efficacy of Inhibition of GH release in a superfused rat pituitary system. In the present application all the 14 peptides tested at 30 nM have a % inhibition above 39 at 120 minutes. In the

WO95/16707 case only peptides 1, 5, 18, 23, 24,and 28 out of 38 reach this value. At 60 minutes the 14 peptides of the present invention are all superior to the peptides of WO95/16707 in this test.

Table III deals with K_1 values and Relative Affinities of hGH-RH Antagonists. In the present invention all of the K_1 values are lower and the RA values are higher than those in the WO95/16707 table, with exception of Peptides 1 and 5.

Table IV is even more significant than the results of Tables II and III. This is an in vivo test. In the present invention all 8 of the peptides tested showed a strong antagonistic activity in the range of 68-95% in the short term (5 min after administration), and good long-term potency. Peptides 3 and 11 while less potent in the short term, were found to be extremely effective in the long term. In the WO 95/16707 case only peptides 1, 18 and 19 were tested with respect to their short-term antagonistic activity 5 min after the administration (Tables IV and V) and their long-term effects were not assessed. Although the nature of the disclosure in WO 95/16707 is somewhat different than in the present invention, the antagonistic activities of the three peptides tested can be calculated to be 56% for Peptide 1, 26% for Peptide 18, and 92% for Peptide 19, when administered at the same dose as the peptides of the present invention. In conclusion, one single peptide (Peptide 19) of WO 95/16707 has a strong antagonistic activity comparable to the peptides of the present invention in the short term, and the potency of this peptide on the long term was not investigated and not proven.

The superiority of the peptides of the present invention becomes even more obvious when the results of the in vitro superfusion tests, receptor binding assays and in vivo tests for GH-RH antagonistic activity are taken together and examined in conjunction to each other. Such an examination is necessary since some of the peptides could exert only weak and unsatisfactory inhibition of GH release in vivo, in spite of having strong GH inhibitory potencies in vitro and high binding affinities towards the GH-RH receptor. For example, even though Peptide 18 of WO 95/16707 caused strong inhibition of GH release in the superfusion test in vitro, in only exerted a 26% inhibition of GH release in vivo; 5 min after its administration; and Peptide 1 of WO 95/16707, in spite of displaying a high receptor binding affinity, only caused a 56% inhibition of GH release in vivo. Thus, the real value of GH-RH antagonists provided in a particular invention can only be judged by a simultaneous comparison of all the test results. In this respect, the present invention teaches 7 peptides (Peptides 1, 2, 3, 4, 9, 11, and 16) with high potencies in all 3 tests, while only one peptide (Peptide 19) of WO 95/16707 fulfills all three criteria. The scope of our invention was not to merely provide antagonists with good activities in one particular test, but to find those amino acid substitutions that assure that the peptides will be potent antagonists in a range of tests, both in vitro and in vivo.

With respect to the Examiner's comment that "WO 95/16707 specifically teaches at pages 21 and 22 that hGH-RH antagonists can be used in suppressing GH level

(instant claim 9), treating cancer (instant claim 10), and inhibiting IGF-II (instant claim 11). Therefore, it would have been obvious... ...to test if the hGH-RH analogs taught by both Sato et al (see Table 1, Figure 1) and WO 95/16707 (see pages 5 and 6) have efficacy in suppressing GH level, treating cancer, and inhibiting IGF-II." As we have shown above, only one peptide (Peptide 19) out of 38 peptides claimed in WO 95/16707 has high inhibitory activity on GH release both in vitro and in vivo, and the long-term efficacy of this peptide in vivo has not been proven. Thus while the potential applications of GH-RH antagonists might be obvious, it is not obvious which chemical structures assure favorable pharmacological effects. Furthermore, neither WO 95/16707 nor Sato et al show the actual efficacy of the peptides described there in treating cancer or inhibiting IGF-II. In fact, Sato does not mention at all the possible application of GH-RH antagonists for treating cancer or inhibiting IGF-II. However we would like to draw the attention of the Examiner to Table VII and Figure III of the present application and to the paper of Szepeshazi K et al (Br. J. Cancer 82: 1724-1731, 2000) where three peptides of the present invention (Peptide 1 or JV-1-36; Peptide 9 or JV-1-10; and Peptide 11) were compared to Peptide 19 (that is MZ-4-71) of WO 95/16707 which, as discussed above, is probably the most potent antagonist described in that invention. As shown in Table VII and Figure III of the present application and in Fig. 1C and Table 1 of the mentioned paper, when the nude mice bearing xenografts of HT-29 human colon cancer were treated with GH-RH antagonists given as single daily s.c. injections at a dose of 20 μg/day, Peptide 1 and Peptide 9 of this invention significantly inhibited the tumor growth, in contrast to Peptide 19 of WO 95/16707 which had no significant inhibitory effect. The concentrations of IGF-II peptide and the expression levels of its mRNA were also more potently suppressed by Peptide 1 (JV-1-36) of the present invention than by Peptide 19 (MZ-4-71) of WO 95/16707 (see Table 1. in Szepeshazi et al).

It is clear however that the superior properties of the compounds used in claims 9-11 would not be suggested to one skilled in the art by reviewing the WO95/16707 disclosure.

With respect to Sato, it is correct that this reference does disclose that certain changes in structure affect antagonistic activity. It should be noted however that there is NO in vivo testing in Sato and Sato merely advocates changing 7 out of the 19 positions indicated as changeable in the present claims. Thus there is nothing in Sato to suggest the peptides of the present application or they superior qualities in use as found by applicants. Furthermore nothing is gained by combining the teachings of WO95/16707 and Sato to lead one skilled in the art to carry out the invention of the present application.

This application does not deal with the methodology of making peptides in this class but rather the finding that certain substitution patterns lead to SUPERIOR activity, particularly in the area of affinity for receptor sites , strong and protracted/prolonged inhibition of GH release in vitro and in vivo, and antitumor effect.

The Examiner has failed to show that these superior activities would have been obvious to one skilled in the art at the time the invention was made.

Finally, it is submitted that Examiner's sentence bridging pages 8 and 9 of the outstanding Official Action is merely a rewording of the long discredited "obvious to try argument". It has long been established that for references to form effective bases for a 35 USC 103 rejection, they must, per se, or in combination, actually suggest the invention set forth in the claims. As stated above, the Examiner has not met this criterion and thus this Honorable Board is respectfully solicited to reverse the Examiner on this ground of rejection.

Conclusion

In view of the foregoing arguments and the amendment submitted herewith, It is appellants' position that all claims in the application are patentable. It is therefore requested that the Examiner be reversed on all grounds of rejection and the application be remanded to her for passage to issue,

Respectfully submitted

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Appendix

Claims on appeal

Claim 9. A method of suppressing excessive levels of GH in a patient in need of same which comprises administering to said patient an effective amount of a peptide selected from the group having the formulae:

X-R^1-R^2-Asp-Ala-R^5-R^6-Thr-R^8-R^9-R^{10}-Arg-R^{12}-R^{13}-R^{14}-R^{15}-R^{16}-Leu-R^{18}-R^{19}-Arg-R^{21}-R^{22}-Leu-Gln-Asp-Ile-R^{27}-R^{28}-R^{29}-NH_2

wherein X is PhAc, IndAc, or Nac,

R^1 is Tyr or His,

R^2 is D-Arg [or D-Cit],

R^5 is Ile or Val,

R^6 is Phe, Nal or Phe(Y), in which Y= Cl,

R^8 is Asn, Gln, Ala, or D-Asn,

R^9 is Arg, Har, Lys, Orn, D-Arg, D-Har, D-Lys, D-Orn, Cit, Nle, Tyr (Me), Ser, Ala or Aib,

R^{10} is Tyr or or Tyr(Me),

R^{12} is Lys,

R^{13} is Val or Nle,

R^{14} is Leu or Nle,

R^{15} is Gly, Ala, Abu, Nle or Gln,

R^{16} is Gln or Arg,

R^{18} is Ser or Nle,

R^{19} is Ala ,

R^{21} is Lys ,

R^{22} is Leu, Ala or Aib,

R^{27} is Met, Leu, Nle, Abu, or D-Arg,

R^{28} is Arg, D-Arg, or Ser,

R^{29} is Arg, D-Arg, Har or D-Har,

provided that where R^9 and R^{28} are Ser, R^{29} is other than Arg or Har,

and pharmaceutically acceptable salts thereof .

Claim 10. A method of treating a patient having a cancer carrying receptors for IGF-I or –II which comprises administering to said patient an effective amount of a peptide selected from the group having the formulae:

X-R^1-R^2-Asp-Ala-R^5-R^6-Thr-R^8-R^9-R^{10}-Arg-R^{12}-R^{13}-R^{14}-R^{15}-R^{16}-Leu-R^{18}-R^{19}-Arg-R^{21}-R^{22}-Leu-Gln-Asp-Ile-R^{27}-R^{28}-R^{29}-NH_2

wherein X is PhAc, IndAc, or Nac,

R^1 is Tyr or His,

R^2 is D-Arg [or D-Cit],

R^5 is Ile or Val,

R^6 is Phe, Nal or Phe(Y), in which Y= Cl,

R^8 is Asn, Gln, Ala, or D-Asn,

R^9 is Arg, Har, Lys, Orn, D-Arg, D-Har, D-Lys, D-Orn, Cit, Nle, Tyr (Me), Ser, Ala or Aib,

R^{10} is Tyr or or Tyr(Me),

R^{12} is Lys,

R^{13} is Val or Nle,

R^{14} is Leu or Nle,

R^{15} is Gly, Ala, Abu, Nle or Gln,

R^{16} is Gln or Arg,

R^{18} is Ser or Nle,

R^{19} is Ala ,

R^{21} is Lys ,

R^{22} is Leu, Ala or Aib,

R^{27} is Met, Leu, Nle, Abu, or D-Arg,

R^{28} is Arg, D-Arg, or Ser,

R^{29} is Arg, D-Arg, Har or D-Har,

provided that where R^9 and R^{28} are Ser, R^{29} is other than Arg or Har,

and pharmaceutically acceptable salts thereof .

Claim 11. A method for inhibiting IGF-II levels in tumors (cancers) and the expression of mRNA for IGF-II in the same tumors in patients having such tumors, which comprises administering to said patient an effective amount a peptide selected from the group having the formulae:

X-R^1-R^2-Asp-Ala-R^5-R^6-Thr-R^8-R^9-R^{10}-Arg-R^{12}-R^{13}-R^{14}-R^{15}-R^{16}-Leu-R^{18}-R^{19}-Arg-R^{21}-R^{22}-Leu-Gln-Asp-Ile-R^{27}-R^{28}-R^{29}-NH_2

wherein X is PhAc, IndAc, or Nac,

R^1 is Tyr or His,

R^2 is D-Arg [or D-Cit],

R^5 is Ile or Val,

R^6 is Phe, Nal or Phe(Y), in which Y= Cl,

R^8 is Asn, Gln, Ala, or D-Asn,

R^9 is Arg, Har, Lys, Orn, D-Arg, D-Har, D-Lys, D-Orn, Cit, Nle, Tyr (Me), Ser, Ala or Aib,

R^{10} is Tyr or or Tyr(Me),

R^{12} is Lys,

R^{13} is Val or Nle,

R^{14} is Leu or Nle,

R^{15} is Gly, Ala, Abu, Nle or Gln,

R^{16} is Gln or Arg,

R^{18} is Ser or Nle,

R^{19} is Ala ,

R^{21} is Lys ,

R^{22} is Leu, Ala or Aib,

R^{27} is Met, Leu, Nle, Abu, or D-Arg,

R^{28} is Arg, D-Arg, or Ser,

R^{29} is Arg, D-Arg, Har or D-Har,

provided that where R^9 and R^{28} are Ser, R^{29} is other than Arg or Har,

and pharmaceutically acceptable salts thereof .

Claim 12. The method of claim 9 which comprises administering a compound having the formula [$PhAc^0$, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-$RH(1-29)NH_2$ Peptide 1.

Claim 13. The method of claim 9 which comprises administering a compound having the formula [$PhAc^0$, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-$RH(1-29)NH_2$ Peptide 3.

Claim 14. The method of claim 10 which comprises administering a compound having the formula [$PhAc^0$, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-$RH(1-29)NH_2$ Peptide 1.

Claim 15. The method of claim 10 which comprises administering a compound having the formula [$PhAc^0$, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-$RH(1-29)NH_2$ Peptide 3.

Claim 16. The method of claim 11 which comprises administering a compound having the formula [$PhAc^0$, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-$RH(1-29)NH_2$ Peptide 1.

Claim 17. The method of claim 11 which comprises administering a compound having the formula [$PhAc^0$, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-$RH(1-29)NH_2$ Peptide 3.